Supported and liquid phase task specific ionic liquids for base catalysed Knoevenagel reactions

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Abstract

A series of Hünig's base tethered ammonium ionic liquids have been used to catalyse the Knoevenagel condensation of aldehydes/ketones with malononitrile and ethyl cyanoacetate. The reactions were performed under homogeneous and under biphasic, liquid–liquid and liquid–silica supported ionic liquid, conditions with the biphasic systems employing cyclohexene as the second phase. By increasing the distance between the ammonium head group and Hünig's base the activity of the catalyst was found to increase. Higher activity, in general, was found under homogeneous reaction conditions; however, the recyclability of the catalyst was improved by supporting the BIL under biphasic conditions.
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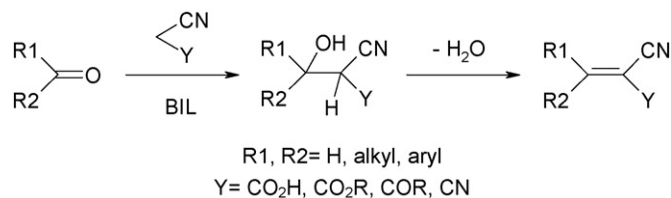
1. Introduction

Base catalysed transformations are frequently used both on small scale as well as large scale in organic synthesis for example in aldol [1], Knoevenagel [2], Henry [3] and Michael [4] reactions. To catalyse these process organic amines, alkali alkoxides, and alkali hydroxides are commonly used as a homogeneous phase with the reagents. Although effective, these reagents are difficult to separate and, in many cases, are not recycled. To alleviate this problem, solid basic catalysts have been developed utilizing either inorganic solid materials, such as base metal oxides and carbonates, or by supporting organic bases, for example amines, on inorganic or polymeric supports. This approach has attracted intense interest and has been reviewed extensively [5]. Effective heterogeneous base catalysis have been found for aldol [6], Knoevenagel [7], Henry [8] and Michael [9] reactions and, in many, cases the solid base is recyclable.

Within the family of base catalysed reactions for fine chemical synthesis, the Knoevenagel condensation is widely employed to synthesize intermediates of fine chemicals. This reaction allows the formation of a C=C double bond from carbonyl compounds and active methylene groups (Scheme 1). For example, the condensation of carbonyl compounds and methylene malonic esters produce several important key industrial products which include nitriles used in anionic polymerization, α,β-unsaturated ester intermediates employed in the synthesis of several therapeutic drugs, for example niphendipine and nitrendipine [10], and pharmacological products, for example calcium channel blockers and antihypertensives may also be produced using this reaction [11]. A wide range of bases can be employed for this condensation; however, alkali metal hydroxides and pyridine as well as other amines such as ethylenediamine and piperidine are the most studied [12]. A wide range of solid catalysts and solid-supported catalysts have also been applied to this reaction such as anion-exchange resins [13], KF [14], magnesium and aluminum oxides, [15] alkali-exchanged and alkali-encapsulated zeolites [16], hydrotalcites [17], amino group-immobilized silica materials [18], clays [19], alkali and alkaline earth carbonates [20], nitridated aluminosilicates and aluminophosphates [21], and porous silicate quaternary ammonium composites [22].

Recently, ionic liquid technology has been utilized to enable base catalysed reactions to occur allowing the base to be recycled and, in some cases, showing higher selectivities compared with

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Scheme 1. Base-catalysed Knoevenagel condensation reaction.

Table 1
Textural characteristics of silica and silica with basic ionic liquids

Sample	S_{BET} (m^2 g^{-1})	Pore diameter (nm)
SiO$_2$ (pH = 4)	287	16
BIL1/SiO$_2$	139	17
BIL2/SiO$_2$	149	17
BIL3/SiO$_2$	142	17

molecular solvents. For example, L-proline has been reported to act as a recyclable chiral base in ionic liquids in the chiral aldol condensations between propanone and a range of aromatic and aliphatic aldehydes [23]. In addition, Forsyth and co-workers have demonstrated that in ionic liquids based on [NTf$_2$]$^-$ and [FAP]$^-$ significantly higher selectivities are found at high conversion for aldol condensation of 4-*t*-butylbenzaldehyde and propanal to form 3-(4-*t*-butyl-phenyl)-2-methyl-propenal, using piperidine compared with either the industrial process or using piperidine in molecular solvents [24]. Ionic liquids have also been used in combination with solid supports. The Knoevenagel reaction has been performed in ionic liquids catalysed by hydrotalcite achieving excellent conversions after 1 h [25]. Shen et al., immobilized a functionalized imidazolium ionic liquid on to silica gel, producing a solvent free recyclable system for the Knoevenagel condensation and for the cycloadditon of CO$_2$ with propylene [26]. For each reaction conversions in excess of 90% were reported with a slight decrease upon recycle. Recently, guanidine based ionic liquids have been developed and employed as catalysts for the aldol [27], Henry [28], and Knoevenagel [29] reactions without any loss in catalytic activity after 15 runs. Amino-acids such as glycine and proline [30] have also been used as a promoter in imidazolium ionic liquids for the condensation of aliphatic and aromatic aldehydes with malononitrile and diethylmalonate at 35–55 °C leading to high conversions albeit over a period of 12–48 h.

Herein, we report the Knoevenagel reaction mediated by recyclable basic ionic liquid (BIL) using the methodology of task specific ionic liquids pioneered by Davis et al. [31]. The ionic liquids used are derivatives of the non-nucleophilic Hünig's base tethered to an alkyl ammonium side chain. The cations are shown in Fig. 1 and in each case the counter ion used was bis{(trifluoromethyl)sulfonyl}imide ([NTf$_2$]$^-$). These ionic liquids were employed as the solvent/catalyst, supported on silica
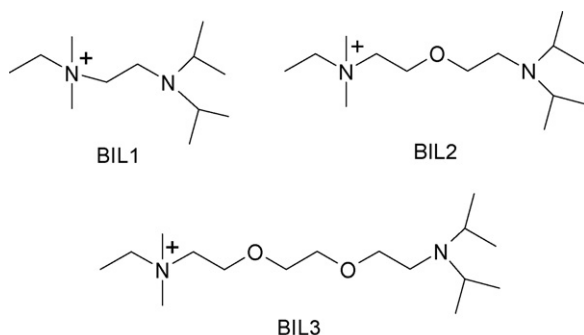

Fig. 1. Structure of the basic ionic liquids (BILs) used in this study.

suspended in an organic solvent and as a biphasic system with the BIL in catalytic amounts.

2. Experimental

2.1. Materials

Unless otherwise stated all reagents (*ex* Aldrich) were used as received. 1-Butyl-1-methylpyrrolidinium bis{(trifluoromethyl)sulfonyl}imide ([C$_4$mpyrr][NTf$_2$]), 1-butyl-3-methylimidazoluim bis{(trifluoromethyl)sulfonyl}imide ([C$_4$mim][NTf$_2$]) and 1-butyl-2,3-dimethylimidazoiumium bis{(trifluoromethyl)sulfonyl}imide ([C$_4$dmim][NTf$_2$]) were prepared in house using standard literature methods [32]. The synthesis and the characteristics of the task specific basic ionic liquids BIL1, BIL2 and BIL3 have previously been reported [33]. In all cases, prior to reaction, the ionic liquids were dried under vacuum at 50 °C overnight. All ionic liquids contained <0.16 wt% water determined by Karl-Fischer analysis and <5 ppm halide by suppressed ion chromatography.

2.2. Preparation and characterisation of the silica supported BIL catalyst

In the case of the silica supported BILs, the catalysts were prepared by stirring 0.35 g of silica (DAVICAT, pH 4, 7 and 10, Davidson Catalysts) and 0.19 mmol of BIL dissolved in 3 cm^3 of methanol. The solvent was removed under vacuum and the BIL/silica was left to dry overnight under vacuum at 50 °C. The BET surface areas and the DRIFTS of the samples formed are shown in Table 1 and Fig. 2, respectively. As expected, after adsorption of the BIL, the BET surface area of the support decreased due to some pore blocking; this is also shown in the small increase in average pore diameter. The DRIFTS were taken on a Bruker Equinox 55 spectrometer, operating at a resolution of 4 cm^{-1} using the mirror as the background. A comparison of the DRIFT spectra from the silica and the silica supported BILs clearly shows additional bands at ~2970 cm^{-1}. These bands are also present in the pure BILs and are due to CH stretching vibrations, as found in other ionic liquid systems [34], indicating the presence of the BIL on the surface of the silica.

2.3. Homogeneous reaction procedure

Typically, malononitrile (0.138 g, 2.09 mmol) or ethyl cyanoacetate (0.235 g, 2.09 mmol) was added to 0.19 mmol of BIL either at room temperature or, in the case of malononitrile,
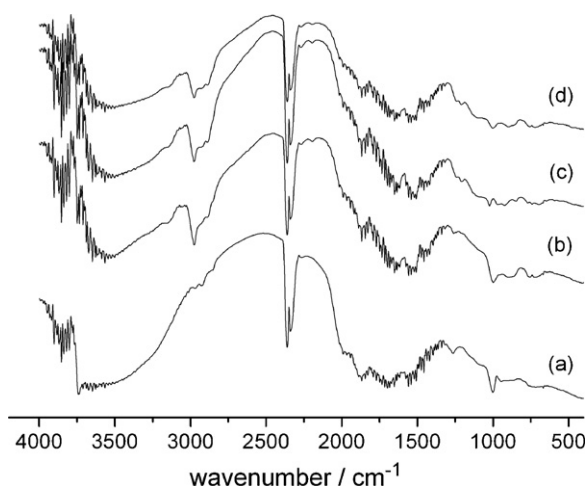
Fig. 2. Comparison of the DRIFT spectra of (a) silica (pH 4), (b) BIL1/SiO$_2$, (c) BIL2/SiO$_2$ and (d) BIL3/SiO$_2$ using the mirror as the background.

2.4. Heterogeneous reaction procedure

For reactions under biphasic liquid conditions, typically, 0.19 mmol of BIL was stirred with 7 cm^3 of cyclohexene before the addition of malononitrile (0.138 g, 2.09 mmol) and then benzaldehyde (0.201 g, 1.9 mmol) at room temperature. Following reaction, the cyclohexene was decanted and the BIL was washed twice with 7 cm^3 cyclohexene and the remaining ionic liquid recycled.

For reactions with the silica supported BILs, typically, 0.35 g of silica and 0.19 mmol of BIL was suspended in 7 cm^3 of cyclohexene before the addition of malononitrile (0.138 g, 2.09 mmol) followed by benzaldehyde (0.201 g, 1.9 mmol) whilst stirring at room temperature. After completion of the reaction, the cyclohexene was decanted and the BIL/SiO$_2$ washed twice with 7 cm^3 cyclohexene and the catalyst recycled.

A range of solvents were tested for the liquid–liquid reactions including ethyl acetate, THF, cyclohexane, toluene and diethyl ether; however, only cyclohexene fulfilled the criteria of solubilising the reagents and products without dissolving the BIL. Although cyclohexene was used as solvent, there was no spectral evidence for the formation of Michael adducts with the activated methylene substrates.

2.5. Analysis

All heterogeneous reactions were analysed directly with decane as an internal standard, using a Hewlett-Packard 6890 Gas Chromatograph equipped with a zebron ZB-5 column and a flame ionization detector. All homogeneous reactions were analysed in the same manner after direct distillation or solvent extraction from the reaction media. Products were identified by Perkin-Elmer Clarus 500 GCMS using a PE-5MS column.

at 50 °C to ensure complete dissolution before being allowed to cool to room temperature. To this reaction mixture benzaldehyde (0.201 g, 1.9 mmol) was added and the solution stirred at 750 rpm for the desired time period at room temperature. On completion of the reaction, the products and starting materials were removed either by direct distillation under vacuum at 100 °C and 0.1 mbar using a Kugelrohr Büchi glass oven B-550, or by solvent extraction using cyclohexene in a volume ratio 1:7 (BIL:cyclohexene), repeated three times. In both cases, ^{1}H NMR indicated that <5 mol% of the reagents/products remained in the ionic liquid following workup. For the recycle experiments, the separated ionic liquid was dried under vacuum at 50 °C, recharged with reagents and the reaction repeated.

Table 2
Comparison of the conversion for the Knoevenagel reaction of aldehydes and ketones with methylene nucleophiles at room temperature under homogeneous reaction conditions using the basic ionic liquid at 10 mol% with respect to carbonyl compound

Entry	R1	R2	Y	Ionic liquid	Time	Conv. (%)
1	H	C$_6$H$_{13}$	CO$_2$Et	BIL1	60 min	50
2	H	C$_6$H$_{13}$	CO$_2$Et	BIL2	20 min	87
3	H	C$_6$H$_{13}$	CO$_2$Et	BIL3	20 min	91
4	H	C$_6$H$_{13}$	CO$_2$Et	[C$_4$mpyrr][NTf$_2$]	24 h	40
5	H	C$_6$H$_{13}$	CO$_2$Et	[C$_4$mim][NTf$_2$]	24 h	7
6	H	C$_6$H$_{13}$	CO$_2$Et	[C$_4$dmim][NTf$_2$]	24 h	30
7	H	C$_4$H$_9$	CN	BIL2	30 min	100
8	H	C$_4$H$_9$	CO$_2$Et	BIL2	30 min	89
9	H	C$_6$H$_{13}$	CN	BIL2	30 min	99
10	H	C$_6$H$_{13}$	CO$_2$Et	BIL2	30 min	100
11	H	Ph	CN	BIL2	30 min	100
12	H	Ph	CO$_2$Et	BIL2	30 min	100
13	CH$_3$	C$_2$H$_5$	CN	BIL2	30 min	64
14	CH$_3$	C$_2$H$_5$	CO$_2$Et	BIL2	30 min	0
15	CH$_3$	C$_3$H$_7$	CN	BIL2	30 min	82
16	CH$_3$	C$_3$H$_7$	CO$_2$Et	BIL2	30 min	0
17	C$_2$H$_5$	C$_4$H$_9$	CN	BIL2	30 min	27
18	C$_2$H$_5$	C$_4$H$_9$	CO$_2$Et	BIL2	30 min	0
19		−cC$_5$H$_{10}$−	CN	BIL2	30 min	84
20		−cC$_5$H$_{10}$−	CO$_2$Et	BIL2	30 min	10

3. Results and discussion

3.1. Homogeneous reactions

Table 2 (entries 1–6) summarises the results from the reaction between heptaldehyde and ethylcyanoacetate as a function of the three basic ionic liquids, shown in Fig. 1, compared with the reaction in three non-basic ionic liquids in the absence of any catalyst. In each case the reaction was carried out using 10 mol% IL with respect to heptaldehyde. Using [C$_4$mpyrr][NTf$_2$], [C$_4$mim][NTf$_2$] and [C$_4$dmim][NTf$_2$], the reaction was slow in comparison with the BILs, for example reaching 7–40% conversion in 24 h compared with >50% in 20 min to 1 h with the BILs. A comparison of the time variation of the reaction in the BILs, Table 2 entries 1–3, shows that the activity of BIL1 < BIL2 ~ BIL3. This is inline with the hypothesis that by increasing spacer length between the cationic ammonium centre and the Hünig's base, the base strength increases [33]. Although this may be due to decreasing steric hindrance around the amine centre, due to the presence of bulky diisopropyl groups, it is more likely that the increasing base strength and activity is due to decreased Coulombic repulsion on protonation of the Hünig's centre with the ammonium centre. Importantly, for BILs with a sufficiently long tether, i.e. BIL2 and BIL3, comparable activity to that for free Hünig's base under solventless conditions is found which showed 89% conversion after 20 min.

Entries 7–20 in Table 2 show the conversions using BIL2 at 10 mol% with respect to carbonyl for the Knoevenagel condensations of a range of aldehydes and ketones with ethyl cyanoacetate or malononitrile. Within 30 min, the majority of aldehydes reacted with both malononitrile and ethyl cyanoacetate to give almost quantitative conversion to the desired product. As reported for molecular solvent reactions [9], the analogous reactions with ketones were found to be slower using the basic ionic liquid due to the general reactivities of aldehydes and ketones. This finding is also in accordance with Ranu et al. who noted that ketones were less reactive than aldehydes even when using a much stronger basic ionic liquid, [C$_4$mim][OH]. Therein, a range of aldehydes produced condensation products in excess of 80% after 10 min of reaction whereas the ketones required up to 2 h achieving similar conversions [35]. Predictably, in all cases condensations with malononitrile (pK_a ~ 11.5) resulted in higher yields than those using ethyl cyanoacetate (pK_a ~ 9). For example, the conversions of butanone, pentan-2-one and 3-heptanone with malononitrile were 64% (entry 13), 82% (entry 15) and 27% (entry 17), respectively, whereas no reaction was observed with ethyl cyanoacetate under identical conditions. A similar observation was reported by Forbes et al. using 20 mol% glycine in [C$_2$mim][NTf$_2$] [30]. For all reactions the only product observed was the corresponding substituted alkene. Whilst the homogenous systems give excellent conversions in short reaction times, solidification of the reaction mixture made product extraction difficult without catalyst degradation or leaching. To alleviate this difficult workup, the use of the BIL in a biphasic liquid–liquid system as well as supported on silica was examined. In both cases cyclohexene was used as the solvent in which the substrates/products are soluble but the reaction takes place in the basic ionic liquid phase. To evaluate the advantages and disadvantages of each system, BIL2 was employed as the catalyst.

Table 3

Comparison of the conversion for the Knoevenagel reaction of aldehydes and ketones with methylene nucleophiles at room temperature under liquid–liquid and solid–liquid reaction conditions using the basic ionic liquid at 10 mol% with respect to carbonyl compound

Entry	R1	R2	Y	System	Time (h)	Conv. (%)
1	H	Ph	CN	Solid–liquid	1	96
2	H	Ph	CN	Liquid–liquid	1	90
3	H	Ph	CO$_2$Et	Solid–liquid	1	72[a]
4	H	Ph	CO$_2$Et	Liquid–liquid	1	71[b]
5	H	C$_4$H$_9$	CN	Solid–liquid	1	100
6	H	C$_4$H$_9$	CN	Liquid–liquid	1	100
7	H	C$_4$H$_9$	CO$_2$Et	Solid–liquid	1	100
8	H	C$_4$H$_9$	CO$_2$Et	Liquid–liquid	1	100
9	H	C$_6$H$_{13}$	CN	Solid–liquid	0.5(1)	74(80)
10	H	C$_6$H$_{13}$	CN	Liquid–liquid	0.5(1)	42(43)
11	H	C$_6$H$_{13}$	CO$_2$Et	Solid–liquid	0.5(1)	68(74)
12	H	C$_6$H$_{13}$	CO$_2$Et	Liquid–liquid	0.5(1)	40(44)
13		–cC$_5$H$_{10}$–		CN	Solid–liquid	0.5(1)	90(92)
14		–cC$_5$H$_{10}$–		CN	Liquid–liquid	0.5(1)	77(78)
15		–cC$_5$H$_{10}$–		CO$_2$Et	Solid–liquid	24	<20
16		–cC$_5$H$_{10}$–		CO$_2$Et	Liquid–liquid	24	<20
17	C$_2$H$_5$	C$_4$H$_9$	CN	Solid–liquid	0.5(1)	48(59)
18	C$_2$H$_5$	C$_4$H$_9$	CN	Liquid–liquid	0.5(1)	9(20)
19	CH$_3$	C$_3$H$_7$	CN	Solid–liquid	0.5(1)	92(98)
20	CH$_3$	C$_3$H$_7$	CN	Liquid–liquid	0.5(1)	54(67)
21	CH$_3$	C$_2$H$_5$	CN	Solid–liquid	0.5(1)	70(73)
22	CH$_3$	C$_2$H$_5$	CN	Liquid–liquid	0.5(1)	42(52)

[a] 72% conversion of which 22% was alcohol intermediate.

[b] 71% conversion of which 24% was alcohol intermediate.

3.2. Heterogeneous reactions

An important variable for the silica supported BILs is the surface acidity of the support used. Silica's with pH 4, 7 and 10 used to support BIL2 and were found to give 75, 52 and 43% conversion, respectively, for the reaction between benzaldehyde and ethyl cyanoacetate after 30 min. In the case of pH 4 silica supported BIL, the catalysts remains dispersed throughout the reaction. In contrast, with pH 7 and 10 silica supported BILs, the solid aggregated in the reaction mixture leading to a loss in surface area and hence a decrease in conversion. This aggregation is thought to be due to a reduced Coulombic interaction between the BIL and silica. Some reaction was observed in the absence of the BIL with 14 and 34% conversion found for the silica with pH 7 and 10 after 30 min under analogous conditions, respectively. Importantly, silica with pH 4 did not catalyse the Knoevenagel condensation even after extended reaction times without the presence of BIL and, therefore, was used to study the effect of supporting the BIL.

Table 3 summarises the results of a range of Knoevenagel condensations using both silica supported BIL2 and the biphasic BIL2-cyclohexene system. As found with the homogeneous reactions, the aldehyde substrates were generally more reactive towards malononitrile than ketones and little or no conversions were noted for reactions between ketones and ethyl cyanoacetate. Similar conversions for the condensation of a range of aromatic aldehydes with malononitrile were reported by Song and co-workers using the biphasic system 1-(2-aminoethyl)-3-methylimidazolium tetrafluoroborate/water [36].

In the case of the aldehyde substrates the liquid–liquid and solid–liquid systems showed slightly lower activity than the analogous homogeneous systems. For example, the condensation of heptaldehyde with malononitrile after 30 min showed 42% conversion in the liquid–liquid system (Table 3, entry 10) and 74% conversion in the solid–liquid system (Table 3 entry 9). In comparison, after 30 min in the homogeneous system 99% conversion (Table 2, entry 9) was recorded using BIL2. A similar pattern was observed for the condensation of heptaldehyde with ethyl cyanoacetate, 40% conversion was found using the liquid–liquid system (Table 3, entry 12) and 68% conversion using the solid–liquid system (Table 3, entry 11) after 30 min compared with 100% using the homogeneous reaction conditions (Table 2, entry 10). Interestingly, during the solid–liquid and liquid–liquid catalysed reactions of benzaldehyde and ethyl-cyanoacetate the alcohol intermediate (Scheme 1) was also observed by GCMS prior to dehydration. This intermediate was not observed in the homogeneous reaction and to the best of our knowledge has not been reported previously.

A decrease in the activity between the homogeneous and liquid–liquid reaction systems was also observed for the condensation reactions involving ketones. For example, after 30 min the condensation of 3-heptanone with malononitrile produced 9% conversion in the liquid–liquid system (Table 3, entry 18) compared with 27% under homogeneous reaction conditions (Table 2, entry 17). However, on supporting BIL2 on silica a significant increase in the activity was observed with 48% conversion found after 30 min (Table 3, entry 17). This was found to
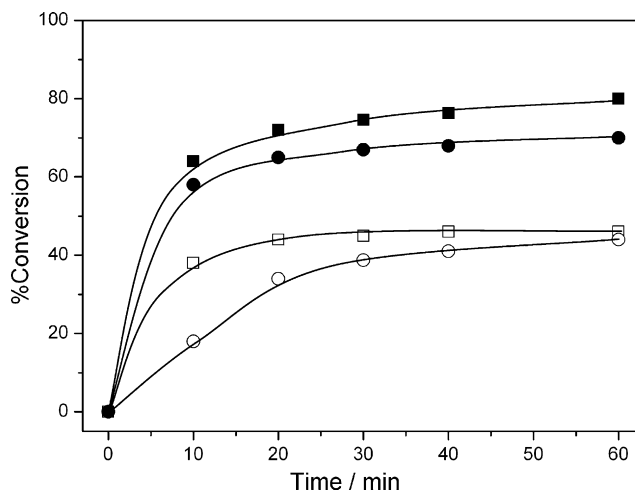

Fig. 3. Percentage conversion of heptaldehyde during the Knoevenagel reaction with malononitrile (squares) and ethyl cyanoacetate (circles) under liquid–liquid (open symbols) and solid–liquid (closed symbols) reaction conditions as a function of time.

be a general trend for the ketone substrates. For example, for the condensation of butanone with malononitrile; 64% conversion is observed for the homogeneous reaction (Table 2, entry 13) and 42% conversion for the liquid–liquid reaction (Table 3, entry 22), whereas using the silica supported BIL the conversion increased to 70% (Table 3, entry 21) after 30 min. Similarly, the reaction between pentan-2-one and malononitrile showed an increase in the conversion from 54 to 92% after 30 min upon the addition of silica to the liquid–liquid reaction (Table 3, entries 19–20) compared with 82% conversion was observed after 30 min (Table 2, entry 15) obtained under homogeneous reaction conditions.

3.3. Reaction kinetics

For all of the solid–liquid and liquid–liquid reactions, little or no increase in conversion is observed between 30 and
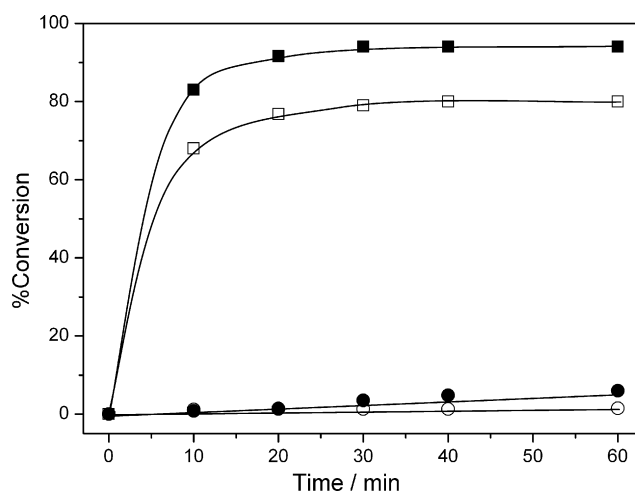

Fig. 4. Percentage conversion of cyclohexanone during the Knoevenagel reaction with malononitrile (squares) and ethyl cyanoacetate (circles) under liquid–liquid (open symbols) and solid–liquid (closed symbols) reaction conditions as a function of time.
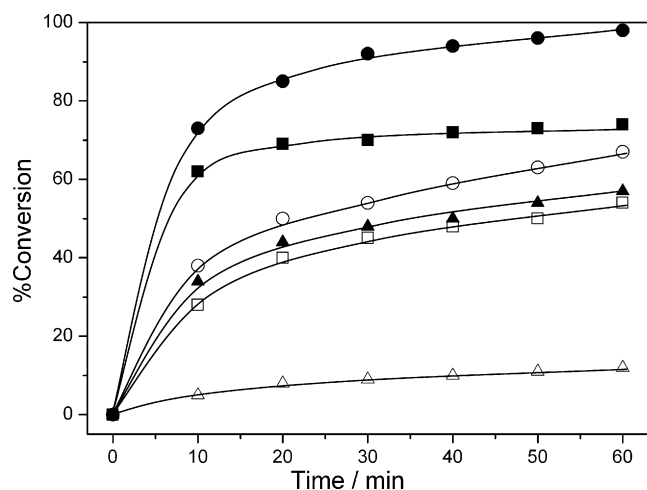
Fig. 5. Percentage conversion of butanone (squares), pentan-2-one (circles) and heptan-3-one (triangles) during the Knoevenagel reaction with malononitrile under liquid–liquid (open symbols) and solid–liquid (closed symbols) reaction conditions as a function of time.

60 min reaction time (Table 3, entries 9–14, 17–22). In order to examine this effect in more detail, comparative kinetic studies were performed for the liquid–liquid and solid–liquid systems. Figs. 3–5 show the time variation for heptaldehyde, cyclohexanone, butanone, pentan-2-one and heptan-3-one with malononitrile and heptaldehyde with ethyl cyanoacetate. In all cases adsorbing BIL2 on silica led to an increase in the rate as well as the overall conversion compared with the liquid–liquid system. This large increase in initial rate is thought to be due to the larger exposed surface area of the BIL when adsorbed on the silica compared with the liquid–liquid system. Although the initial rates are high, it is clear that in many cases the conversion levels drop off after 20–30 min, irrespective of the catalyst system used. Catalyst deactivation by product poisoning was disregarded as the addition of a mole equivalent of product to the initial reaction containing heptaldehyde and ethylcyanoacetate resulted in ~70% conversion in the solid–liquid system after 1 h, i.e. similar to that found in the absence of product. The limitation on the conversion reached is thought to be due to the secondary reaction resulting in hydrolysis of the cyano group(s) on the nucleophile (Scheme 2), forming a carboxylic acid which binds to the catalyst causing deactivation the catalyst and loss of substrate. Although the ionic liquid and reagents were
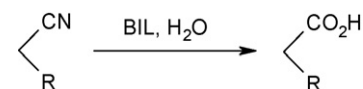
Scheme 2. Hydrolysis of nitriles to form the corresponding carboxylic acid.

dried prior to reaction, the reaction produces water as a byproduct and thus hydrolysis increases as the reaction proceeds. This hypothesis is supported by the fact that using the liquid–liquid reaction conditions, 100% conversion was obtained after 90 min for the reaction of heptaldehyde and diethylmalonate, i.e. using a nucleophile which cannot hydrolyse.

3.4. Recycles

Direct distillation following the reaction of heptaldehyde and ethyl cyanoacetate under homogeneous reaction conditions of BIL2 was performed at 100 °C under 0.1 mbar. However, this workup procedure resulted in a drop in activity from 100 to 44% conversion after 20 min. Analysis of the BIL following distillation using ^{1}H NMR showed that significant degradation of the catalyst had occurred and, therefore, all subsequent workups and recycles were performed using solvent extraction using cyclohexene. Table 4 (entry 1) shows the effect of recycling BIL2 for the reaction of heptaldehyde with malononitrile under homogeneous reaction conditions. A gradual decrease in conversion was observed on recycle of the BIL with 100% conversion found for the first reaction after 30 min but only 20% conversion observed after four reactions. A similar trend was also observed for the reaction between heptan-3-one and malononitrile (Table 4, entry 4). In this case, although some conversion was found on the first reaction, after 3 recycles the catalyst showed no significant activity.

One possible explanation for the poor catalyst recycle following extraction is the presence of the water formed during the condensation remaining in the ionic liquid. However, similar results were obtained even if the ionic liquid was dried under vacuum between reactions. The ^{1}H NMR of BIL2 after reaction indicated some degradation which is thought to be due to thermal degradation as, although the reactions were performed at room temperature, the exothermicity of the reaction causes the reaction mixture to rise to ~65 °C, even with rapid stirring. Another possible explanation is that the catalyst leaches during workup. However, analysis of the solvent phase after extraction

Table 4

Comparison of recycles between homogeneous, liquid–liquid and solid–liquid systems for the Knoevenagel condensation between heptaldehyde and heptan-3-one with malononitrile

Entry	R1	R2	System	Time (min)	% Conversion Run				
					1	2	3	4	5
1	H	C_6H_{13}	Homogeneous	20	100	99	50	20	8
2	H	C_6H_{13}	Liquid–liquid	60	46	41	45	40	42
3	H	C_6H_{13}	Solid–liquid	60	73	71	76	71	75
4	C_2H_5	C_4H_9	Homogeneous	35	27	10	3	0	0
5	C_2H_5	C_4H_9	Liquid–liquid	60	20	17	19	22	21
6	C_2H_5	C_4H_9	Solid–liquid	60	59	55	66	64	62

by suppressed ion chromatography (IC), showed that the leaching of BIL into cyclohexene was below the detection limit, i.e. <1 ppm. Interestingly, Ranu et al. also reported that after five recycles of [C$_4$mim][OH] for the homogeneous Knoevenagel reaction, the ionic liquid volume had to be increased by 50% with fresh catalyst in order to maintain the activity [35].

Table 4 also compares the recycle efficiency of the homogeneous reaction system with that under liquid–liquid and solid–liquid catalysed reaction conditions for the reaction of malononitrile with heptaldehyde and heptan-3-one. Although in some cases a significant loss in activity was observed for the homogeneous BIL, when dispersed on a solid or in a solvent, little change in activity was observed on recycle. Using the dispersed BIL the exothermic nature of the reaction will be reduced by the high heat capacity of the silica, in the case of the silica supported BIL, and by the presence of the molecular solvent which can absorb the heat in both the solid–liquid and liquid–liquid systems. In addition, the reduced rate of reaction will allow the heat to be dispersed more efficiently. Importantly, the removal of the product is more efficient in the dispersed system compared with the reaction under homogeneous conditions. In the latter the reaction mixture becomes solid whereas under liquid–liquid and solid–liquid reaction conditions the cyclohexene enables the mixture to remain liquid throughout the reaction due to continual extraction/removal of the product. As shown by the decreased overall conversion during the reaction, some water remains with the catalyst and causes inhibition; however, this material is easily extracted with fresh cyclohexene as part of the workup restoring the initial activity. As found with the homogeneous reaction system, ion chromatography showed no leaching of the ionic liquid during the workup. Therefore, although in some cases the homogeneous system has an initially higher activity and higher overall conversion for the first reaction, both the liquid–liquid and solid–liquid catalysed reactions show much better recyclability. A similar observation was also reported using a liquid–liquid reaction system of 1-(2-aminoethyl)-3-methylimidazolium tetrafluoroborate/water and water for the reaction of benzaldehyde and ethyl cyanoacetate. Therein, no loss in catalytic activity after six recycles was found [36].

4. Conclusions

Task specific basic ionic liquids have been shown to facilitate the Knoevenagel condensation reaction of a range of carbonyl molecules with methylene nucleophiles. Using the basic ionic liquid without solvent produced a homogeneous reaction system and showed high initial activity and overall conversion. However, on recycle, degradation of the IL was observed and it was difficult to remove the entire product by solvent extraction due to the reaction mixture solidifying which results in loss of activity on subsequent reactions. Supporting the basic ionic liquid in an immiscible solvent or on a silica support reduces the initial activity, in general; however, in both cases, excellent recyclability was with the reaction repeated over five times without leaching of the ionic liquid into the extractant phase or reduction in activity.

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